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=> d his

     (FILE 'HOME' ENTERED AT 19:07:18 ON 17 APR 2003)

     FILE 'MEDLINE, CAPLUS, BIOSIS, SCISEARCH' ENTERED AT 19:07:31 ON 17 APR
     2003
L1         76851 S (KNOCKOUT OR NULL OR DISRUPT?)(9A)(MOUSE OR MICE OR RODENT)
L2          7910 S (KNOCKOUT OR NULL OR DISRUPT?)(9A)(SQUIRREL OR RAT OR WOODCHU
L3           757 S (KNOCKOUT OR NULL OR DISRUPT?)(9A)(VOLE OR MARMOT OR HAMSTER
L4         84925 S L1 OR L2 OR L3
L5         23112 S HOMOLOGOUS(W)RECOMBINATION
L6         17443 S (EMBRYONIC(W)STEM OR ES)(W)CELL
L7          2217 S L4 AND L5
L8           940 S L7 AND L6
L9       2154638 S (DIFFICULT? OR PROBLEM OR PITFALL OR DISADVANTAGE)
L10           24 S L8 AND L9
L11           14 DUP REM L10 (10 DUPLICATES REMOVED)

=>  d bib ab 1-14 l11

L11  ANSWER 1 OF 14     MEDLINE                          DUPLICATE 1
AN   2003097754     IN-PROCESS
DN   22497738   PubMed ID: 12577066
TI   Homologous recombination in human embryonic
     stem cells.
AU   Zwaka Thomas P; Thomson James A
CS   National Primate Research Center and the Department of Anatomy, University
     of Wisconsin - Madison Medical School, Madison, WI 53715.
SO   NATURE BIOTECHNOLOGY, (2003 Mar) 21 (3) 319-21.
     Journal code: 9604648. ISSN: 1087-0156.
CY   United States
DT   Journal; Article; (JOURNAL ARTICLE)
LA   English
FS   IN-PROCESS; NONINDEXED; Priority Journals
ED   Entered STN: 20030302
     Last Updated on STN: 20030302
AB   Homologous recombination applied to mouse embryonic
     stem (ES) cells has revolutionized the study of gene
     function in mammals.  Although most often used to generate
     knockout mice, homologous
     recombination has also been applied in mouse ES
     cells allowed to differentiate in vitro.  Homologous
     recombination is an essential technique if human ES
     cells are to fulfill their promise as a basic research tool.  It
     also has important implications for ES cell-based
     transplantation and gene therapies.  Significant differences between mouse
     and human ES cells have hampered the development of
     homologous recombination in human ES
     cells.  High, stable transfection efficiencies in human ES
     cells have been difficult to achieve, and, in
     particular, electroporation protocols established for mouse ES
     cells work poorly in human ES cells.  Also, in
     contrast to their murine counterparts, human ES cells
     cannot be cloned efficiently from single cells, making it
     difficult to screen for rare recombination events.  Here we report
     an electroporation approach, based on the physical characteristics of
     human ES cells, that we used to successfully target
     HPRT1, the gene encoding hypoxanthine phosphoribosyltransferase-1 (HPRT1),
     and POU5F1, the gene encoding octamer-binding transcription factor 4
     (Oct4; also known as POU domain, class 5, transcription factor 1
     (POU5F1)).

L11  ANSWER 2 OF 14     MEDLINE                          DUPLICATE 2
```

AN 2002337976 MEDLINE
DN 22075709 PubMed ID: 12079755
TI **Knockout mice**: simple solutions to the **problems** of genetic background and flanking genes.
AU Wolfer David P; Crusio Wim E; Lipp Hans Peter
CS Institute of Anatomy and Center for Neuroscience, University of Zurich, Winterthurerstrasse 190, CH-8057 Zurich, Switzerland.
SO TRENDS IN NEUROSCIENCES, (2002 Jul) 25 (7) 336-40. Ref: 33
Journal code: 7808616. ISSN: 0166-2236.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200208
ED Entered STN: 20020625
Last Updated on STN: 20020815
Entered Medline: 20020814
AB Inducing null mutations by means of **homologous recombination** provides a powerful technique to investigate gene function and has found wide application in many different fields. However, it was realized some time ago that the specific way in which such knockout mutants are generated can be confounding, making it impossible to separate the effects of the induced null mutation from those of alleles originating from the **embryonic stem cell** donor. In addition, effects from null mutations can be altered on different genetic backgrounds. Here we present some simple breeding strategies to test for flanking gene effects that are compatible with the recommendations of the Banbury Conference on Genetic Background in **Mice** and with common practices of creating and maintaining **mouse knockout** lines.

L11 ANSWER 3 OF 14 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2002:415104 BIOSIS
DN PREV200200415104
TI Outline for generation and analysis of opioid receptor **knockout mice**.
AU Sora, Ichiro (1); Ikeda, Kazutaka (1); Mishina, Yuji (1)
CS (1) Graduate School of Medicine, Department of Neuroscience, Division of Psychobiology, Tohoku University, Sendai, 980-8574 Japan
SO Folia Pharmacologica Japonica, (July, 2002) Vol. 120, No. 1, pp. 47-54. print.
ISSN: 0015-5691.
DT General Review
LA Japanese
AB **Knockout** transgenic **mice** of opioid receptors make it possible to analyze molecular mechanisms of opioid receptors that could not be done by traditional pharmacological techniques. Generation of **knockout mice** requires a variety of technologies such as molecular genetics, cell biology, and embryology. Making **knockout mice** also requires a long period of labor-intensive work. **Knockout mice** can be obtained after several experimental steps: constructing a targeting vector, introduction of the vector into **embryonic stem cell**, and generation of the chimeric animal. Special attention may be required for behavioral and biochemical analyses of **knockout mice**. This review will be focused on the outline and **pitfalls** for audiences who are interested in analysis of existing **knockout mice** as well as making new ones.

L11 ANSWER 4 OF 14 CAPLUS COPYRIGHT 2003 ACS DUPLICATE 3
AN 2001:862125 CAPLUS
DN 136:335617

TI Contemporary gene targeting strategies for the novice
AU Cheah, Siew-Sim; Behringer, Richard R.
CS Department of Molecular Genetics, The University of Texas M. D. Anderson Cancer Center, Houston, TX, 77030, USA
SO Molecular Biotechnology (2001), 19(3), 297-304
CODEN: MLBOEO; ISSN: 1073-6085
PB Humana Press Inc.
DT Journal; General Review
LA English
AB A review. Gene targeting in mouse embryonic stem (**ES**) **cells** is a fundamental methodol. for generating mice with precise genetic modifications. Although there are many complex gene targeting strategies for creating a variety of diverse mutations in **mice**, most investigators initially choose to generate a **null** allele. Here we provide a guide for the novice to generate a null allele for a protein coding gene using a fundamental gene targeting strategy. Ultimately, a well considered gene targeting strategy saves significant amts. of time, money, and research animal lives. The straightforward strategy presented here bypasses many of the **pitfalls** assocd. with gene knockouts generated by novices. This guide also serves as a foundation for subsequently designing more complex gene targeting strategies.
RE.CNT 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 5 OF 14 SCISEARCH COPYRIGHT 2003 ISI (R)
AN 1998:872174 SCISEARCH
GA The Genuine Article (R) Number: 138BD
TI Modifiable gene expression in mice: Kidney-specific deletion of a target gene via the Cre-loxP system
AU Stec D E; Sigmund C D (Reprint)
CS UNIV IOWA, COLL MED, DEPT INTERNAL MED & PHYSIOL & BIOPHYS, TRANSGEN & GENE TARGETING FACIL, IOWA CITY, IA 52242 (Reprint); UNIV IOWA, COLL MED, DEPT INTERNAL MED, TRANSGEN & GENE TARGETING FACIL, IOWA CITY, IA 52242
CYA USA
SO EXPERIMENTAL NEPHROLOGY, (NOV-DEC 1998) Vol. 6, No. 6, pp. 568-575.
Publisher: KARGER, ALLSCHWILERSTRASSE 10, CH-4009 BASEL, SWITZERLAND.
ISSN: 1018-7782.
DT Article; Journal
FS CLIN
LA English
REC Reference Count: 41
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB With the advent of gene-targeting in **mouse** embryonic stem (**ES**) **cells**, the use of **knockout mice** to study the physiological effects of loss of gene function has become increasingly prevalent. However, there are several drawbacks with conventional gene-targeting approaches which may make phenotyping of the resultant mice **difficult**, if not, impossible. Conventional gene-targeting results in the loss of function of the targeted gene in all cells and tissues, which can be problematic for genes which are required developmentally, which exhibit a wide tissue-specific expression pattern, or are part of complex paracrine systems. As with mice that lack the angiotensinogen or endothelin-1 gene, loss of gene function may lead to a lethal phenotype which can be manifested during embryonic development, at birth or postnatally. These limitations could potentially be circumvented by using a system in which the loss of gene function is placed under spatial and/or temporal control. Wt: will discuss how the cre-loxP recombinase system can be applied to delete a gene in a tissue- and developmentally regulated fashion.

L11 ANSWER 6 OF 14 MEDLINE
AN 1998058811 MEDLINE
DN 98058811 PubMed ID: 9371842

TI Disruption of the m1 receptor gene ablates muscarinic receptor-dependent M current regulation and seizure activity in mice.
CM Comment in: Proc Natl Acad Sci U S A. 1999 Oct 26;96(22):12222-3
AU Hamilton S E; Loose M D; Qi M; Levey A I; Hille B; McKnight G S; Idzerda R L; Nathanson N M
CS Department of Pharmacology, University of Washington School of Medicine, Seattle 98195-7750, USA.
NC 5T32HL07312 (NHLBI)
NS26920 (NINDS)
NS30454 (NINDS)
+
SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1997 Nov 25) 94 (24) 13311-6.
Journal code: 7505876. ISSN: 0027-8424.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199801
ED Entered STN: 19980122
Last Updated on STN: 20000327
Entered Medline: 19980108
AB Muscarinic acetylcholine receptors are members of the G protein-coupled receptor superfamily expressed in neurons, cardiomyocytes, smooth muscle, and a variety of epithelia. Five subtypes of muscarinic acetylcholine receptors have been discovered by molecular cloning, but their pharmacological similarities and frequent colocalization make it **difficult** to assign functional roles for individual subtypes in specific neuronal responses. We have used gene targeting by **homologous recombination** in **embryonic stem cells** to produce mice lacking the m1 receptor. These mice show no obvious behavioral or histological defects, and the m2, m3, and m4 receptors continue to be expressed in brain with no evidence of compensatory induction. However, the robust suppression of the M-current potassium channel activity evoked by muscarinic agonists in sympathetic ganglion neurons is completely lost in m1 mutant mice. In addition, both homozygous and heterozygous mutant mice are highly resistant to the seizures produced by systemic administration of the muscarinic agonist pilocarpine. Thus, the m1 receptor subtype mediates M current modulation in sympathetic neurons and induction of seizure activity in the pilocarpine model of epilepsy.

L11 ANSWER 7 OF 14 MEDLINE
AN 97259978 MEDLINE
DN 97259978 PubMed ID: 9106077
TI Gene targeting in **embryonic stem cells**: the new physiology and metabolism.
AU Moreadith R W; Radford N B
CS Molecular Cardiology Laboratories, University of Texas Southwestern Medical Center, Dallas 75235-8573, USA.
NC P41-RR02584 (NCRR)
RO1-51568
SO JOURNAL OF MOLECULAR MEDICINE, (1997 Mar) 75 (3) 208-16. Ref: 81
Journal code: 9504370. ISSN: 0946-2716.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW LITERATURE)
LA English
FS Priority Journals
EM 199706
ED Entered STN: 19970630
Last Updated on STN: 19970630
Entered Medline: 19970619

AB The development of transgenic technology, whereby genes (or mutations) can be stably introduced into the germline of experimental mammals, now allows investigators to create mice of virtually any genotype and to assess the consequences of these mutations in the context of a developing and intact mammal. In contrast to traditional "gain-of-function" mutations, typically created by microinjection of the gene of interest into the one-celled zygote, gene targeting via **homologous recombination** in pluripotential **embryonic stem cells** allows one to modify precisely the gene of interest. The purpose of this review is to introduce the reader to the history of development of **embryonic stem cell** technology, the current methods employed to create "knock-out" mice, and the application of these methods to solve **problems** in biology. While the technology promises to provide enormous insight into mammalian development genetics, our desire is that this review will stimulate the application of gene targeting in **embryonic stem cells** to begin to unravel **problems** in complex regulatory pathways, specifically intermediary metabolism and physiology.

L11 ANSWER 8 OF 14 MEDLINE
AN 96312456 MEDLINE
DN 96312456 PubMed ID: 8698242
TI Inactivation of the mouse Brca1 gene leads to failure in the morphogenesis of the egg cylinder in early postimplantation development.
AU Liu C Y; Flesken-Nikitin A; Li S; Zeng Y; Lee W H
CS Center for Molecular Medicine/Institute of Biotechnology, The University of Texas Health Science Center at San Antonio 78245, USA.
NC CA58318 (NCI)
P50-CA58183 (NCI)
SO GENES AND DEVELOPMENT, (1996 Jul 15) 10 (14) 1835-43.
Journal code: 8711660. ISSN: 0890-9369.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199609
ED Entered STN: 19960912
Last Updated on STN: 19960912
Entered Medline: 19960905
AB BRCA1 is proposed to be a tumor suppressor gene. To explore the biological function of BRCA1, a partial deletion (amino acids 300-361) of mouse Brca1 exon 11 was introduced into the genome of embryonic stem (**ES**) **cells** by **homologous recombination** . Mice carrying one mutated allele of Brca1 appear normal and are fertile up to 10 months of age without any sign of illness. However, no viable progeny homozygous for the Brca1 mutant allele were obtained. Detailed analysis of large numbers of embryos at different stages of development indicated that the homozygous mutant concepti are severely retarded in growth as early as embryonic day 4.5 (E4.5) and are resorbed completely by E8.5. Although the homozygotes at E5.5-E6.5 are able to synthesize DNA and display distinguishable embryonic and extraembryonic structures, they fail to differentiate and form egg cylinders. Consequently, they were unable to form primitive streaks and undergo gastrulation. Consistent with these in vivo results, blastocysts homozygous for mutated Brca1 alleles are at a considerable **disadvantage** when grown in vitro. These observations suggest that Brca1 has an important role in the early development of mouse embryos.

L11 ANSWER 9 OF 14 MEDLINE DUPLICATE 4
AN 96181372 MEDLINE
DN 96181372 PubMed ID: 8631315
TI Repair-deficient 3-methyladenine DNA glycosylase homozygous mutant mouse cells have increased sensitivity to alkylation-induced chromosome damage and cell killing.

AU Engelward B P; Dreslin A; Christensen J; Huszar D; Kurahara C; Samson L
CS Department of Molecular and Cellular Toxicology, Harvard School of Public Health, Boston, Massachusetts 02115, USA.
NC CA 55042 (NCI)
P01-ES03926 (NIEHS)
SO EMBO JOURNAL, (1996 Feb 15) 15 (4) 945-52.
Journal code: 8208664. ISSN: 0261-4189.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199607
ED Entered STN: 19960715
Last Updated on STN: 19960715
Entered Medline: 19960702
AB In Escherichia coli, the repair of 3-methyladenine (3MeA) DNA lesions prevents alkylation-induced cell death because unrepaired 3MeA blocks DNA replication. Whether this lesion is cytotoxic to mammalian cells has been **difficult** to establish in the absence of 3MeA repair-deficient cell lines. We previously isolated and characterized a mouse 3MeA DNA glycosylase cDNA (Aag) that provides resistance to killing by alkylating agents in E. coli. To determine the in vivo role of Aag, we cloned a large fragment of the Aag gene and used it to create Aag-deficient mouse cells by targeted **homologous recombination**. Aag null cells have no detectable Aag transcripts or 3MeA DNA glycosylase activity. The loss of Aag renders cells significantly more sensitive to methyl methanesulfonate-induced chromosome damage, and to cell killing induced by two methylating agents, one of which produces almost exclusively 3MeAs. Aag null **embryonic stem cells** become sensitive to two cancer chemotherapeutic alkylating agents, namely 1,3-bis(2-chloroethyl)-1-nitrosourea and mitomycin C, indicating that Aag status is an important determinant of cellular resistance to these agents. We conclude that this mammalian 3MeA DNA glycosylase plays a pivotal role in preventing alkylation-induced chromosome damage and cytotoxicity.

L11 ANSWER 10 OF 14 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 1997:156028 BIOSIS
DN PREV199799455231
TI Germline transmission in IL-9 **knockout mice**: A practical approach to intrastrain and interstrain variability.
AU Bagic, Anto
CS USUHS, Microbiol Immunol., 4301 Jones Bridge Rd., Bethesda, MD 20814-4799 USA
SO Croatian Medical Journal, (1996) Vol. 37, No. 4, pp. 245-253.
ISSN: 0353-9504.
DT Article
LA English
AB Aim. Analysis and comparison of the contribution of 129 and C57BL/6 (BL/6-III) embryonic stem (**ES**) **cell** clones in the coat and germline of chimeras, and development of a strategy to optimize germline transmission. Methods. Interleukin-9 gene was inactivated in 129 and C57BL/6 (BL/6-III) **ES cells** using a gene-targeting technique, and two confirmed clones from each cell background were injected into C57BL/6 and BALB/cByJ blastocysts, respectively. After reexpansion, the injected 3.5 days post coitum (dpc) embryos were orthotopically transferred into the uterus of 2.5 dpc pseudopregnant foster mothers. The pups were born seventeen days later. At three weeks of age, they were weaned, ear-tagged, and the level of coat chimerism was visually assessed. At 7 weeks, male chimeras were test-mated for germline transmission with females of the host-embryo background, and the transmission was confirmed on the basis of coat color of the F-1 offspring. Results. Two 129 clones, 1F6 and 3G1, containing IL-9 gene mutated by **homologous recombination**, were identified. 106 (1F6) and 112 (3G1) C57BL/6 blastocysts were injected and 16 (12

males) and 17 (13 males) chimeras identified, respectively. Ten male chimeras from 1F6 clone transmitted the IL-9 mutation in the germline and produced brown (strain 129 origin) pups after mating with C57BL/6 (black) females. In contrast, none of the 13 male chimeras from 3G1 clone were germline chimeras. From 104 (3G9) and 107 (3E11) BALB/cByJ blastocysts injected with BL/6-III clones, we obtained 7 (2 males) and 3 (all males) chimeras respectively, and of these, none transferred the IL-9 mutation in the germline. Conclusions. Our data confirm the importance of proper testing of the parental cell line and all derived clones with respect to germline transmission. Intrastrain and interstrain variability remains the main obstacle to germline chimera production. However, new approaches to this **problem** may significantly increase the level of success.

L11 ANSWER 11 OF 14 MEDLINE
AN 96400507 MEDLINE
DN 96400507 PubMed ID: 8806883
TI Aryl-hydrocarbon receptor-deficient mice are resistant to 2,3,7,8-tetrachlorodibenzo-p-dioxin-induced toxicity.
AU Fernandez-Salguero P M; Hilbert D M; Rudikoff S; Ward J M; Gonzalez F J
CS Laboratory of Molecular Carcinogenesis, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892, USA.
SO TOXICOLOGY AND APPLIED PHARMACOLOGY, (1996 Sep) 140 (1) 173-9. Journal code: 0416575. ISSN: 0041-008X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199610
ED Entered STN: 19961219
Last Updated on STN: 19961219
Entered Medline: 19961031
AB Acute exposure of mammals to the environmental pollutant 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) results in a diverse set of toxicologic and pathologic effects. The mechanism of some of these effects has been studied extensively in vitro and correlative studies have indicated the involvement of a transcription factor known as the aryl hydrocarbon receptor (AHR). However, a definitive association of the AHR with TCDD-mediated toxicity has been **difficult** to establish due to the diversity of effects and the ubiquitous expression of this receptor. In an effort to distinguish AHR-mediated TCDD toxicities from those resulting from alternative pathways, we have made use of the recently described AHR-deficient mouse that was generated by locus-specific **homologous recombination** in **embryonic stem cells**. Present studies demonstrate that AHR-deficient mice are relatively unaffected by doses of TCDD (2000 micrograms/kg) 10-fold higher than that found to induce severe toxic and pathologic effects in littermates expressing a functional AHR. Analyses of liver, thymus, heart, kidney, pancreas, spleen, lymph nodes, and uterus from AHR-deficient mice identified no significant TCDD-induced lesions. The resistance of AHR-deficient mice to TCDD-induced thymic atrophy appears restricted to processes involving AHR since the corticosteroid dexamethasone rapidly and efficiently induced cortical depletion in both AHR-deficient and normal littermate control mice. Taken together these results suggest that the pathological changes induced by TCDD in the liver and thymus are mediated entirely by the AHR. However, it is important to note that at high doses of TCDD, AHR-deficient mice displayed limited vasculitis and scattered single cell necrosis in their lungs and livers, respectively. The mechanism(s) responsible for these apparently receptor-independent processes remain unclear but may involve novel, alternative pathways for TCDD-induced toxicity.

L11 ANSWER 12 OF 14 MEDLINE
AN 96208768 MEDLINE
DN 96208768 PubMed ID: 8645566

TI Role of platelet-derived growth factors in mouse development.
AU Betsholtz C
CS Department of Medical Biochemistry, University of Goteborg, Sweden.
SO INTERNATIONAL JOURNAL OF DEVELOPMENTAL BIOLOGY, (1995 Oct) 39 (5) 817-25.
Ref: 76
Journal code: 8917470. ISSN: 0214-6282.
CY Spain
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199607
ED Entered STN: 19960805
Last Updated on STN: 20000303
Entered Medline: 19960725
AB The current understanding of platelet-derived growth factor (PDGF) physiological functions in vivo is discussed in the context of mouse development. In particular, the review focuses on recent experiments in which genetic approaches have been applied in order to mutate the PDGF and PDGF receptor genes in the mouse. Thus, the PDGF-B and PDGF beta receptor (PDGFRb) genes were recently inactivated by **homologous recombination** in **embryonic stem cells**. Their phenotypes are highly similar, displaying cardiovascular, hematological and renal defects. The latter is particularly interesting since it consists of a specific cellular defect: the complete loss of kidnety glomerular mesangial cells. As such, the phenotype not only sheds light on the developmental importance of PDGF-B-PDGFRb interactions, but also reveals information about the function of mesangial cells. Based on detailed morphological studies of mutant glomeruli and the absence of urine collection in the urinary bladder, I propose that the mesangial cells function as interior "filter holders", the "filter" consisting of the glomerular basement membrane and associated cell types. The filter holder model would predict that glomerular filtration is critically dependent on an interior structural support of the filter, which is normally provided by the mesangial cells and the mesangial matrix. In addition to the mutants generated by gene targeting, the mouse patch mutation is discussed. This deletion encompasses the PDGFRa locus. The last part of the review focuses on the **problems** encountered when interpreting gene knockout phenotypes in the physiological functions of gene products.

L11 ANSWER 13 OF 14 SCISEARCH COPYRIGHT 2003 ISI (R)
AN 95:566080 SCISEARCH
GA The Genuine Article (R) Number: RP721
TI USE OF TRANSGENICS, NULL MUTANTS, AND ANTISENSE APPROACHES TO STUDY ETHANOLS ACTIONS
AU WEHNER J M (Reprint); BOWERS B J
CS UNIV COLORADO, INST BEHAV GENET, CAMPUS BOX 447, BOULDER, CO, 80309 (Reprint); UNIV COLORADO, SCH PHARM, BOULDER, CO, 80309
CYA USA
SO ALCOHOLISM-CLINICAL AND EXPERIMENTAL RESEARCH, (AUG 1995) Vol. 19, No. 4, pp. 811-820.
ISSN: 0145-6008.
DT Article; Journal
FS LIFE; CLIN
LA ENGLISH
REC Reference Count: 79
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB Behavioral and biochemical responses mediating ethanol's actions have been **difficult** to study in humans and animals because of their complex polygenic nature. Recent progress in the creation of new animal models using recombinant DNA technology has provided a set of genetic tools by which the role of specific candidate genes in ethanol's actions

can be examined. These techniques include the creation of transgenic and **null** mutant **mice**, as well as manipulation of protein synthesis with antisense treatments. These techniques are reviewed, and their potential applications to alcohol research are discussed.

L11 ANSWER 14 OF 14 SCISEARCH COPYRIGHT 2003 ISI (R)
AN 91:161991 SCISEARCH
GA The Genuine Article (R) Number: FC779
TI INTRODUCTION OF A SUBTLE MUTATION INTO THE HOX-2.6 LOCUS IN **EMBRYONIC STEM-CELLS**
AU HASTY P; RAMIREZSOLIS R; KRUMLAUF R; BRADLEY A (Reprint)
CS BAYLOR UNIV, INST MOLEC GENET, 1 BAYLOR PLAZA, HOUSTON, TX, 77030; NATL INST MED RES, LONDON NW7 1AA, ENGLAND
CYA USA; ENGLAND
SO NATURE, (1991) Vol. 350, No. 6315, pp. 243-246.
DT Article; Journal
FS PHYS; LIFE; AGRI
LA ENGLISH
REC Reference Count: 27
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB GENE targeting in embryonic stem (**ES**) **cells** is a powerful tool for generating **mice** with **null** alleles 1. Current methods of gene inactivation in **ES cells** introduce a neomycin gene (neo) cassette both as a mutagen and a selection marker for transfected cells 2-11. Although null alleles are valuable, changes at the nucleotide level of a gene are very important for functional analysis. One gene family in which subtle mutations would be particularly valuable are the clusters of Hox homeobox genes 12-16. Inactivation of genes in a cluster with a neo cassette that includes promoter/enhancer elements may deregulate transcription of neighbouring genes and generate a phenotype which is **difficult** to interpret. We describe here a highly efficient gene targeting method, termed the 'hit and run' procedure. This generates **ES cells** with subtle site-specific mutations with no selectable marker and may be useful for most genes. We have developed this procedure at the hypoxanthine phosphoribosyltransferase (hprt) locus and subsequently isolated **ES cells** with a premature stop codon in the homeobox of Hox-2.6 (ref. 14).